INTERVIEW

Pamela L Kunz, MD

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Tracks 1-15

Select Excerpts from the Interview

Track 4

DR LOVE: Could you comment on some of the ongoing trials evaluating HER2-directed therapies for HER2-positive advanced gastric cancer (GC) or gastroesophageal junction (GEJ) cancer?

DR KUNZ: Different anti-HER2 agents are currently under investigation in advanced GC and GEJ cancer (3.1). Pertuzumab and trastuzumab emtansine (T-DM1) are being investigated in prospective clinical trials. An ongoing prospective study is evaluating triweekly T-DM1 versus weekly T-DM1 or a taxane. It is anticipated that the trial will

complete accrual in about 2 years, but results may not be available for a few more years. We're all excited about the study.

3.1 **Ongoing Phase III Trials of HER2-Directed Therapies in HER2-Positive Locally Advanced or Metastatic Gastroesophageal Junction Cancer or Gastric Adenocarcinoma**

Trial ID	N	Treatment arms
NCT01774786 (BO25114)	780	• Pertuzumab + TFP • Placebo + TFP
NCT00680901 (LOGiC)	545	• Lapatinib + CAPOX • Placebo + CAPOX
NCT01641939 (BO27952)	412	• Triweekly trastuzumab emtansine (3.6 mg/kg) • Weekly trastuzumab emtansine (2.4 mg/kg) • Taxane (paclitaxel or docetaxel)

TFP = trastuzumab, cisplatin and fluoropyrimidine (capecitabine or 5-fluorouracil);
CAPOX = capecitabine/oxaliplatin

www.clinicaltrials.gov. Accessed May 2014.

Tracks 7-8

DR LOVE: Would you discuss the results of the Phase III REGARD and RAINBOW trials of second-line ramucirumab in metastatic GC or GEJ cancer?

DR KUNZ: The REGARD trial of ramucirumab versus placebo demonstrated that accrual to a second-line trial in metastatic GC/GEJ cancer is possible (Fuchs 2014; [3.2]). We're seeing more patients who are eligible to receive second-line therapy. The RAINBOW study of second-line paclitaxel with or without ramucirumab demonstrated that combination therapy was more effective than paclitaxel alone (Wilke 2014; [3.2]). Based on the results of these trials, I believe ramucirumab will be approved (3.3).

3.2 **Efficacy Results of the Phase III REGARD and RAINBOW Trials of Ramucirumab (Ram) in Metastatic Gastroesophageal Junction and Gastric Adenocarcinoma After Disease Progression on First-Line Platinum- and/or Fluoropyrimidine-Containing Combination Therapy**

	REGARD trial[1]		RAINBOW trial[2]	
Clinical outcome	Ram (n = 238)	Placebo (n = 117)	Ram + pac (n = 330)	Pac (n = 335)
Median OS	5.2 mo	3.8 mo	9.6 mo	7.4 mo
p-value	0.047		0.0169	
Median PFS	2.1 mo	1.3 mo	4.4 mo	2.9 mo
p-value	<0.0001		<0.0001	
ORR	3%	3%	28%	16%
p-value	0.76		0.0001	

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; pac = paclitaxel

[1] Fuchs CS et al. *Lancet* 2014;383(9911):31-9; [2] Wilke H et al. Gastrointestinal Cancers Symposium 2014;**Abstract LBA7**.

Most oncologists will combine ramucirumab with other cytotoxic backbones, even without available data. I'm excited about the potential for ramucirumab in combination with other agents.

3.3

Editor's Note: FDA Approves Ramucirumab for Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer

Subsequent to this interview, on April 21, 2014, the FDA approved ramucirumab for use as a single agent for the treatment of advanced or metastatic gastric or GEJ adenocarcinoma that progresses during or after treatment with fluoropyrimidine- or platinum-containing chemotherapy.

www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm394260.htm. Accessed May 27, 2014.

Tracks 9, 12-14

DR LOVE: Can you provide a global view of the key features in the management of neuroendocrine tumors (NETs)?

DR KUNZ: A key decision branch point is to determine if the disease is poorly or well differentiated. It also is important to know whether the disease grade is low, intermediate or high. The Ki-67 value, which is a proliferative index, and the mitotic index are also key features. One needs to ask for these details if they are not included in the pathologist's report because they are important features needed to prognosticate.

These features group patients in different treatment categories. For example, patients with well-differentiated NETs — which include both the low- and intermediate-grade tumors — receive different therapies than those with poorly differentiated NETs. Another major decision branch point is to determine if the tumor is of pancreatic or nonpancreatic origin.

DR LOVE: Does adjuvant therapy have a role in gastrointestinal NET?

DR KUNZ: Currently, even with lymph node-positive disease, adjuvant therapy has no known role. This partly depends on the disease pathology. For a patient with poorly differentiated NET at the time of resection, one would likely offer adjuvant therapy with platinum/etoposide. However, for those with well-differentiated tumors, even with node-positive disease, I would not offer adjuvant therapy.

The Phase II ECOG-E2212 trial will evaluate whether the addition of adjuvant everolimus to the R0 or R1 surgical resection of metastatic pancreatic NETs to the liver will yield improvements in disease-free survival (NCT02031536). Patients will be randomly assigned to receive everolimus or placebo for 1 year. This is exciting because it's the first time the adjuvant question will be asked. I hope that after the completion of that study, we will evaluate the role of adjuvant therapy in earlier settings.

DR LOVE: How do you select patients with NETs for treatment?

DR KUNZ: It is known that adjuvant octreotide controls symptoms of true carcinoid syndrome, like diarrhea and flushing. We also know that somatostatin analogs have an effect on controlling hormones in addition to having antiproliferative effects. The PROMID study of octreotide or placebo for patients with metastatic small-bowel NETs demonstrated a prolonged progression-free survival (PFS) with octreotide (Rinke 2009). So octreotide is my first-line choice for patients with slowly progressive disease.

Also, the Phase III CLARINET study, in patients with nonfunctioning enteropancreatic NETs, demonstrated prolonged PFS with the long-acting aqueous preparation of lanreotide, a slightly different somatostatin analog from octreotide (Caplin 2013). A key take-home message is that patients with progressive disease, hormone-related symptoms or tumor bulk-related symptomatic disease need to be appropriately selected for therapy. For a patient with newly diagnosed metastatic asymptomatic disease with no evidence of progression, I would offer no treatment.

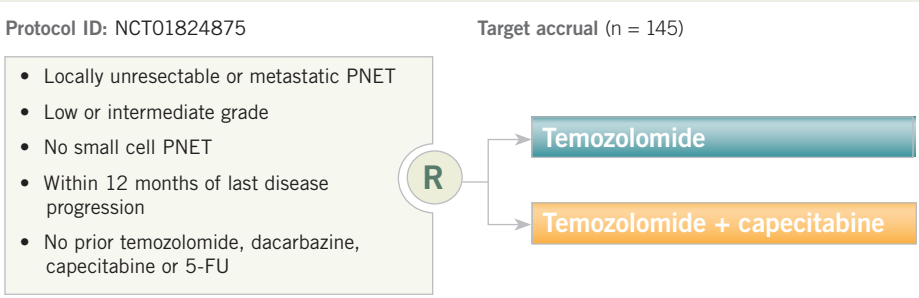
DR LOVE: What's your treatment algorithm for metastatic pancreatic NET?

DR KUNZ: For metastatic NETs of pancreatic origin, the FDA-approved agents are everolimus, an mTOR inhibitor, and sunitinib, a VEGF tyrosine kinase inhibitor. These agents are oral, taken daily and used separately. In comparison to placebo, both showed a 5- to 6-month PFS benefit. The choice of one versus the other sometimes depends on the patient's comorbidities. I will choose sunitinib for a patient with existing hypertension. Everolimus may cause lipid disorders such as hypertriglyceridemia. In a patient with pre-existing lung disorders, everolimus may cause pneumonitis. Streptozocin is the only FDA-approved cytotoxic chemotherapy. It's an alkylating agent thought to have considerable toxicity. Even now, it's not widely available.

We've been trying to look at newer, less toxic cytotoxic therapies. In the past few years, we've been interested in temozolomide, an oral alkylating agent approved for glioblastoma treatment. A retrospective review of the combination of temozolomide with oral capecitabine for 30 patients with metastatic pancreatic NET demonstrated a response rate of 70% (Strosberg 2011). This combination has not been well studied prospectively. A Phase II trial of temozolomide/capecitabine versus temozolomide alone in advanced pancreatic NET is ongoing (3.4). Some believe the combination may be synergistic. ■

3.4

Ongoing Phase II Trial of Temozolomide with or without Capecitabine for Patients with Advanced Pancreatic Neuroendocrine Tumors (PNET)



www.clinicaltrials.gov. Accessed May 2014.

SELECT PUBLICATIONS

Caplin M et al. **A randomized double-blind placebo-controlled study of lanreotide antiproliferative response in patients with enteropancreatic neuro endocrine tumours (CLARINET).** *Proc ESMO* 2013;**Abstract E17-7103**.

Rinke A et al. **Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group.** *J Clin Oncol* 2009;27(28):4656-63.

Strosberg JR et al. **First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas.** *Cancer* 2011;117(2):268-75.